In vivo demonstration that {alpha}-synuclein oligomers are toxic.

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Public Summary:
The aggregation of proteins into oligomers and amyloid fibrils is characteristic of several neurodegenerative diseases, including Parkinson disease (PD). In PD, the process of aggregation of α-synuclein (α-syn) from monomers, via oligomeric intermediates, into amyloid fibrils is considered the disease-causative toxic mechanism. We developed α-syn mutants that promote oligomer or fibril formation and tested the toxicity of these mutants by using a rat lentivirus system to investigate loss of dopaminergic neurons in the substantia nigra. The most severe dopaminergic loss in the substantia nigra is observed in animals with the α-syn variants that form oligomers (i.e., E57K and E35K), whereas the α-syn variants that form fibrils very quickly are less toxic. We show that α-syn oligomers are toxic in vivo and that α-syn oligomers might interact with and potentially disrupt membranes.

Scientific Abstract:
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